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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/836,750	ELIA, JAMES P.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *6-203,206-235 and 240-242* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *236, 238, 239, 244, 247, 250, 251, 253, 257-263, 268-271, 280-285, and 288-290* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/24/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 6-203,206-236,238-242,244,247,250,251,253,257-263,268-271,280-285 and 288-290.

DETAILED ACTION

1. In view of the Appeal Brief filed on 06/01/2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

2. The amendments of 03/02/2009 have been entered in full. Claims 1-5, 204, 205, 237, 243, 245, 246, 248, 249, 252, 254-256, 264-267, 272-279, 286, and 287 are canceled. Claims 6-203, 206-235, and 240-242 remain withdrawn from consideration as being directed to a non-

elected invention. Claims 236, 238, 239, 244, 247, 250, 251, 253, 257-263, 268-271, 280-285, and 288-290 are under examination.

3. In the Appeal Brief filed 06/01/2009 (hereafter, 'Brief'), Applicant has presented separate arguments with respect to claims 236, 238, 239, 244, 247, 250, 251, 253, 257-263, 268-271, and 280-285, and claims 288-290. Applicant asserts that the claims do not stand or fall together. The basis for this distinction, according to Applicant (Brief, p. 46-47), is that claims 288-290 are drawn to the narrowest embodiment of the claimed invention by requiring specific cells, specific sites, and specific modes of administration. The rejection of record finds that the essential elements common to all of the claims are (1) administration of either a stem cell harvested from bone marrow (e.g. claims 261-263, 268, 269), or some factor within Applicant's broad genus of growth factors (claims 236, 238, 239, 244, 247, 250, 251, 253, 257-260, 270, 271, and 280-285,and (2) forming an artery. The rejection further finds that methods comprising these essential and common elements are not enabled by the disclosure, regardless of broad (e.g. "growth factor") or specific (e.g. "living stem cell harvested from bone marrow") limitations. Because no recited limitation rescues any claim from lack of enablement, the entire set of claims under consideration has heretofore been considered as a single group; this practice is continued in the present office action.

4. Applicant (Brief, p. 10) submits that there are three major points to consider when determining whether the instant specification contains a disclosure that would have enabled a skilled person in the medical art to make and use the claimed invention within the purview of the statute. The points are: 1) the content and guidance provided in the specification disclosure; 2) the knowledge in the art at the time the application was filed; and 3) the skill level in the art. The

rejection of record has consistently acknowledged that the level of skill in the art is high. With regard to points 1) and 2), Applicant agrees that the state of the art at the time the instant application was filed did not include any support or disclosure of the growth of new arteries by administering stem cells (Brief, p. 16). Applicant identifies U.S. Patent No. 5,980,887 to Isner et al. (hereinafter "Isner '887"; of record) and the Asahara et al. February 14, 1997 publication in Science entitled, "Isolation of Putative Progenitor Endothelial Cells for Angiogenesis," (hereinafter "Asahara"; of record), and U.S. Patent No. 5,328,470 to Nabel et al. (hereinafter "Nabel" and of record) as examples of the state of the prior art at the time of Applicant's invention (Brief, p. 12). Applicant argues that the instant disclosure distinguishes over prior or contemporary art by employing different cells to achieve different results (Brief, p. 12-13). Applicant further argues that post-filing references confirm Applicant's disclosed and claimed results. Applicant specifically asserts that post-filing publications of record, including Orlic et al. (hereinafter "Orlic"); Strauer et al. (hereinafter "Strauer"); and Dohmann et al. (hereinafter "Dohmann") confirm Appellant's disclosed and claimed results, i.e., heart repair and formation of new cardiac muscle and an artery (Brief, p. 16).

5. This rejection finds that the present application does not provide an enabling disclosure or an accurate prediction of the methods and results that were later achieved by others. Therefore, the post-filing references do not confirm Applicant's disclosed and claimed results but instead, the post-filing references constitute evidence of the further act of invention that was required before achieving any growth of an artery or repair of a heart. This office action will address Applicant's points 1) and 2) along with the predictability or lack thereof in the art, the breadth of the claims, and the quantity of experimentation needed.

6. The breadth of the claims has been addressed in the record. Applicant's election of species, cell, does not change the plain meaning of the words that are still present in the claims. The broadest instant claims (236, 238, 239, 247, 250, 251, 257-259, 261-263, 270,271, and 281-285) recite "growth factor", which according to the specification may be any organic and inorganic matter, bacteria, viruses, proteins, derivatives of cellular products, genes, extracellular matrices, living organisms. Claim 253 recites any gene and any cell. These claims recite non-elected subject matter and, if allowed, they would encompass the entire recited scope regardless of Applicant's species election. It is appropriate and necessary that the entire recited scope should be considered with regard to enablement. While the claims are being discussed primarily with respect to the narrowest embodiments (administration of a stem cell harvested from bone marrow), it must be understood that even if the narrowest claims were enabled (which they are not), such enablement would not extend to the methods that comprise placing any or all of the genus of "growth factors" or all cells, as recited in the claims.

7. As the stated goal of the claimed method includes "growing a new artery in said heart" it is important to consider what the specification teaches about growth of a new artery. Applicant (Brief p. 16) states, "Appellant's specification at pages 54, 56, and 62 clearly defines the claimed term "new artery," and the scope of the claims is legally determined by this disclosure. It is clear from such disclosure what Appellant intended the term "new artery" to mean."

8. For clarity, the relevant sections of pp. 54, 56, and 62 of the specification are reproduced here:

p. 54:

> "After four weeks, another MRI is taken which shows the patient's leg artery. The MRI shows that (1) at the first site a new artery is growing adjacent the patient's

> original leg artery, and (2) at the second site a new section of artery is growing integral with the original artery, i.e., at the second site the new section of artery is lengthening the original artery, much like inserting a new section of hose in a garden hose concentric with the longitudinal axis of the garden hose lengthens the garden hose."

9. This section clearly distinguishes between growth of a *new artery adjacent to* an existing artery and growing a new *section* of an artery *integral with* the original artery. The instant claims recite "growing and integrating a desired artery" which "integrates itself into said body" not "forming a new *section of* an artery." Therefore, the claims are clearly meant to encompass the result predicted or the first site as described above.

> p. 56:
>
> "Anatomic evidence of collateral artery formation is observed by the 30th day following injection to the RAOTS construct. One end of the artery integrates itself in the heart wall to receive blood from the heart. The other end of the artery branches into increasing smaller blood vessels to distribute blood into the heart muscle. Once the growth of the new artery is completed, the new artery is left in place in the heart wall. Transplantation of the new artery is not required."

10. Once again, the "new artery" is described as first forming and then subsequently integrating.

> p. 62:
>
> Similar results are obtained, i.e., a new section of artery grows integral with the original artery, and a new section of artery grows adjacent the original artery. The new section of artery has integrated itself at either end with the original artery so that blood flows through the new section of artery.

11. This section at p. 62 is ambiguous because it refers to two new sections of artery: one integral to existing artery, one adjacent to it. Thus, the antecedent for "the new section of artery" in the second sentence is unclear. Nevertheless, this section of p.62 suggests formation of a new

structure that is not initially integral with the preexisting artery, but which subsequently integrates into an artery, as do each of the relevant sections of p. 54 and p.56.

12. Finally, it is noted that Applicant has acknowledged that the claims were amended from "forming an artery" to "forming a *new* artery" so to define the claimed invention over prior art (Murry et al. of record; Brief, p.21). The basis whereby Applicant's amendment was taken as distinguishing over the prior art is that the insertion of "new" indicated, in light of the instant specification, a process that is different from growth of blood vessel growth by extension from (and integral with) existing arteries in an integral fashion disclosed in Murry et al. Considering all of the evidence, it is reasonable to interpret the claims as encompassing not only extension of new sections of artery from preexisting arteries or arterioles, but also formation of entirely new arterial structures "in the middle of nowhere" so to speak, or *de novo*, in the terminology of the rejection of record.

13. This mechanistic distinction is significant because the art teaches that post-natal arteriogenesis occurs by cell proliferation and remodeling of preexisting collateral arteries or arterioles. See, for example, Buschmann et al., News Physiol Sci. 1999 Jun;14:121-125, at Figure 2, and on p. 122, left column: "Arteriogenesis is the rapid proliferation of preexisting collateral arteries… It is important to recognize that this process is not a passive dilatation but one of active proliferation and remodeling." Thus, by teaching that new arteries, or sections of arteries, will grow adjacent to existing arteries and subsequently integrate, the instant specification teaches a novel process that is at odds with the prevailing understanding in the art. Therefore, prophetic Examples 18 (p.54), 19 (p.56) and 36 (p. 62) are not credible in the absence of a demonstration that such results did or would occur *in vivo*. Therefore, **no claim is enabled**

for a method that causes formation of entirely new arterial structures followed by integration into an existing artery. Furthermore, Applicant assertion that "there can be no doubt that post-filing publications of record… confirm Appellant's disclosed and claimed results, i.e., heart repair and formation of a new artery" (Brief, p.16), is simply not true if "new artery" is defined as in the specification at pages 54, 56, and 62. Although post-filing publications describe methods and results that fall within the scope of the claims under consideration, none of these references support or suggest anything like the formation of a new artery structure which then integrates into an existing artery as taught in the specification.

14. Continuing with the discussion of post-filing references, Applicant states:

> "As evidence in support of the non-enablement rejection, the PTO apparently has relied upon Strauer as establishing that a determination of cell population is critical, citing pages 1916-1917 of the publication. The PTO fails to point to any specific teaching in the record which supports this proposition, and for good reason. Careful review of this publication fails to reveal any teaching that experimentation was required to determine cell population." (Brief, p. 20-21).

15. The rejection of record has pointed out that Strauer et al. 2002 state clearly and in detail that cell population is critical at pp. 1916-1917. This determination of a critical cell population has been held to be an example of the experimentation that would be required before achieving any repair of dead/damaged heart tissue. Strauer et al. state on p. 1916:

> "The most crucial questions we had to address while designing and realizing this trial were: (1) What cell population should we deliver? (2) Which application method is the most efficient? (3) When should the cells be transplanted?" (Emphasis added).

On page 1916, left column, and in the paragraph bridging pages 1916-1917, Strauer et al. reviewed prior work in which various cell fractions were studied or observed to into specific cells types that can contribute to cardiac repair. In so doing, Strauer et al. cited about 20 papers,

all but one of which were published after the filing date of the instant application. (The exception dealt with transplantation of skeletal myoblasts, see ref. 25 in Strauer et al.) It is inexplicable how Applicant could read this and conclude that "Careful review of this publication fails to reveal any teaching that experimentation was required to determine cell population."

16. Applicant's previous attempt to disparage the Strauer et al. 2002 as evidence of the need for experimentation was more accurate. In the Reply Brief filed 03/18/2008, Applicant argued on page 15 that, "it is clear from Strauer 2002 that, at the pages referred to by the Examiner, Strauer 2002 appears to have relied upon the prior work of others, including the selection of cell population, rather than upon experimentation" (Emphasis added here). In response, the rejection mailed on 10/02/2008 included the following: "This is not persuasive, first, because it is still clear that considerable experimentation was done, if not by Strauer then by others, in order to determine the effective cell population." Applicant now asserts that this response was made "without citing any authority" (Brief, p.22). It is clear, however, that the authority relied upon is Applicant's own argument, as shown by the emphasis in the quote above. By asserting that "Strauer appears to have relied upon the prior work of others", Applicant does not persuasively argue that no experimentation was needed; Applicant merely suggests that it was not Strauer et al. who did the experimentation. "Careful review of this publication" reveals that Strauer explicitly teaches that the decision to use the whole mononuclear cell fraction from bone marrow aspirates was made after consideration of several published studies involving various subfractions (paragraph bridging pages 1916-1917). Therefore, Applicant's later statement, "Strauer does not describe using any experimental protocol to determine appropriate cell population, i.e., there is no requirement for using a specific subset of bone marrow stem cells"

(Brief, p. 23, emphasis in original), is misleading. The emphasized conclusion can be reached only in view of Strauer's results and the work of others cited by Strauer. In contrast, the instant specification shows no evidence of awareness that the sub-populations of stem and progenitor cells discussed by Strauer et al. are even a matter of concern.

17. Similarly, Applicant asserts that "Strauer does not disclose that determining time of treatment required experimentation" (Brief, p. 23). Time of treatment was deemed by Strauer et al. to be an important consideration, as noted above and in the record. Again, Strauer et al. considered published results of experimentation performed by others to decide upon a time of administration for their own protocol, which was itself experimental (p.1917, paragraph bridging the columns and next paragraph). The cited references were all published after the filing date of the instant application, except for a 1956 review on wound repair (see refs 35-40 of Strauer et al., 2002). Thus, it is clear that the question of when to administer cells was the subject of much experimentation after the filing of the instant application but prior to the Strauer et al. 2002 publication. Strauer et al. 2002 concluded, "Although the ideal time point for transplantation remains to be defined, it is most likely between days 7 and 14 after the onset of MI" (p.1917, right column. Applicant asserts that a later publication of Strauer et al. ("Strauer 2005" of record) discloses treating chronic MI in patients that had transmural MI some 27 months earlier and that this later publication is the "best evidence" in regard to whether time of treatment in human patients is critical (Brief, p. 23). This shows that *as experimentation continues*, understanding of the process improves. Thus, we find that the instant specification is silent on the subject of timing of cell administration to repair a heart or grow an artery and the "best evidence" in regard to time of treatment only became available approximately 7 years after the

instant application was filed. These facts support the rejection of record, which finds that post-filing references of record, such as Strauer et al. 2002, constitute evidence of the further act of invention that was required before achieving any repair of dead/damaged heart tissue. Any amount of experimentation, such as the work performed or cited by Strauer, regarding what cell population to use, what delivery method to use, and when cells should be transplanted, would be infinitely more than is presented in the instant specification in support of the claimed methods.

18. Further with regard to post-filing references that show evidence of the experimentation required to enable the claimed methods, the rejection of record has pointed out that in peer-reviewed journal articles, failed experiments are generally not reported, and thus when the successful regimen is disclosed, it cannot be concluded that no experimentation was done. Applicant had previously argued that the "Examiner fails to provide evidence that such conduct is commonplace in the medical field, and for good reason. Such rank speculation does not rise to the level of objective evidence" (Reply Brief filed 03/18/2008, page 15). In response, the rejection mailed on 10/02/2008 (paragraph 15) included documented evidence, including a peer-reviewed study and a Web-based forum associated with the highly respected journal, *Nature*, that negative results, unexplained results, "failures", and indeterminate aspects are often not revealed in publications for various reasons. In addition to this documented evidence, the present Examiner took official notice, in view of personal experience as a professional researcher, in support of the statement "In peer-reviewed journal articles, failed experiments are generally not reported, and thus when the successful regimen is disclosed, it cannot be concluded that no experimentation was done". It should be noted the official notice was taken on a matter which had already been established by documented evidence, which is permissible (See MPEP

2144.03). Applicant now urges that the Examiner's taking of official notice "does not rise to the level of evidence" (Brief, p. 25). Even if this is so, the argument presented in paragraph 15 of the rejection mailed on 10/02/2008 stands without the Examiner's official notice. The point being made is simply that when work based on actual experimentation (as opposed to speculation on paper, as in the instant specification) is reported in a scientific journal, not every detail from the laboratory notebook makes it into the final draft. This is well known in the research community, as evidenced by the references cited in the office action mailed on 10/02/2008 (paragraph 15), and it is not "rank speculation" or merely the personal opinion of the Examiner. This is not an accusation of unethical practices or the deliberate withholding of useful data on the part of Dr. Strauer or any other published researcher, as Applicant makes it out be (Brief, p.24). The various reasons need not be unethical or deceptive; they include the practical need of publishers to devote their limited space to communicating the reproducible methods and positive results, resulting in underreporting of the trial-and-error process that lead to the success. Therefore, Applicant has not persuasively argued against the finding that the absence of specific reference to additional experimentation in a peer-reviewed scientific publication cannot be taken as evidence that no additional experimentation was done. There is good reason to believe that relying solely on the printed words in a publication would lead to an underestimation of the amount of work that was actually done. It is conceded, however, that this issue would naturally be more significant in the basic science and preclinical research that is relied upon in designing a clinical trial (such as in the references cited by Strauer et al.), than in a published report of the results a human clinical trial, such as Strauer et al. 2002.

19. A recurring theme in Applicant's arguments concerns the specificity with which the specification is alleged to guide the skilled artisan with regard to the cells to be used in the claimed methods (emphasis added here):

> "One skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that the claimed invention distinguishes from Nabel, Isner '887, and Asahara by describing using **unfractionated (global) bone marrow mononuclear cells** for promoting the growth of arteries.... Appellant's claimed method differs from such existing prior art in regard to the stem cell population, i.e., Appellant's invention requires the transplantation of the **entire array of mononuclear cells** harvested from bone marrow." (Brief, p.13).

> "**Like Appellant**, the three above-mentioned post-filing publications [referring to Orlic, Strauer, and Dohmann] employed the **entire array of bone marrow cellular components**, including stem cells, not an isolated component thereof such as used by Isner '887 and Asahara." (Brief, p.16)

> "Appellant teaches that the **entire array of mononuclear bone marrow cells** contribute to the regeneration of ischemic tissue and such teaching is consistent with Strauer and the Orlic publication cited therein which confirm that mononuclear bone marrow stem cells promote new artery growth." (Brief, p. 21).

> "One skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that the claimed invention distinguishes from Isner '887 by describing using **unfractionated (global) bone marrow mononuclear cells**. As pointed out earlier, there is no basis in fact for the PTO to determine that the instant specification provides guidance to one skilled in the art for implanting anything other than the **entire array of bone marrow derived cells harvested from the patient's bone marrow.** Reading/interpreting the disclosure otherwise is improper because it distorts the reasonable/intended guidance provided to one skilled in the art by Appellant's specification." (Brief, p. 26).

> In regard to Isner '887 and Kornowski et al. U.S. Patent No. 7,097,832 (hereinafter "Kornowski" and of record), only the latter relies upon **the entire array of bone marrow stem cells as claimed in the present application**. Although **Kornowski uses the same population of stem cells as claimed**, Kornowski is not a competent reference due to its filing date. Isner '887, as discussed earlier utilizes a different composition consisting of EC progenitor cells. (Brief, p. 36).

20. Thus, Applicant generally argues that the instant disclosure teaches the use of unfractionated bone marrow in the claimed methods. Certain arguments refer to "stem cell compositions", as if such compositions were recited in the claims. This teaching is allegedly confirmed by post-filing references. These assertions are not supported by the specification. Even if interpreted in Applicant's most favored light, the most precise description of the cells to be administered in the instantly claimed methods is "bone marrow stem cells". **The instant specification refers to bone marrow only in the sentence, "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques"**, which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10). Thus, the specification suggests that three sources of stem cells are equivalent to one another for purposes of the disclosed methods. (The context does not indicate growth of an artery or repair of a heart, but that is a separate issue addressed elsewhere.) The three sources may be expected to comprise overlapping sets of stem cells (of course the stem cells in blood originate in bone marrow) but they are not equivalent to one another, nor are they equivalent to the "unfractionated (global) bone marrow mononuclear cells" or "entire array of bone marrow derived cells harvested from the patient's bone marrow" in Applicant's argument.

21. "Stem cells harvested from cell culture techniques" are not equivalent to "unfractionated (global) bone marrow mononuclear cells". The expression "stem cells harvested from cell culture techniques" does not even limit the original source to bone marrow.

22. "Stem cells harvested from the blood of the patient" are not equivalent to "unfractionated (global) bone marrow mononuclear cells". The expression "stem cells harvested from the blood of the patient" actually teaches away from "unfractionated (global) bone marrow mononuclear

cells". With regard to stem cells harvested from the blood, It was still unclear long after the instant specification was filed whether circulating blood contains any mesenchymal stem cells or other marrow-derived cells with broad potential (Roufosse *et al.*, Int J Biochem Cell Biol. 2004 Apr;36(4):585-597 of record; see especially section 3, pp. 588-591, Table 2, and section 6, p. 394). Therefore, by listing "stem cells harvested from the blood of the patient" as an equally usable alternative of "stem cells harvested from the bone marrow", the specification teaches away from the suggestion that the bone marrow cells should be mesenchymal stem cells. The instant specification does not mention mesenchymal stem cells, even once.

23. "Unfractionated (global) bone marrow mononuclear cells" would *include* stem cells, but the expressions "stem cells harvested from the bone marrow" and "unfractionated (global) bone marrow mononuclear cells" are not equivalent. The expression "unfractionated (global) bone marrow mononuclear cells" necessarily includes all of the bone marrow mononuclear cells, not just stem cells. At the time the instant application was filed, the expressions "stem cells harvested from the bone marrow" and "stem cells harvested from the blood" were typically understood to refer to the CD34+ fraction (Rowley *et al.*, Bone Marrow Transplantation, June 1998, Volume 21, Number 12, Pages 1253-1262, of record; see p. 1253, first three sentences of Summary and top of right column). Similarly, when Janssen *et al.*, (Journal of Hematotherapy, 1:349-359 (1992)) describe use of an apparatus for processing of bone marrow stem cells, the definitive demonstration that "stem cells" were obtained was by identification of CD34+ cells or by colony forming assays; prior to that the cells were simply referred to as fractions obtained in a step of isolation (mononuclear, Ficoll gradient, buffy coat, etc., see Figures 10 and 11 and Table 1). Thus, "*stem cells* harvested from the bone marrow" would be understood to connote a sub-

population of bone marrow cells, not "unfractionated (global) bone marrow mononuclear cells". The instant specification does not indicate that any other meaning was intended. In view the terminology of the art, the recitation of "stem cells harvested from bone marrow", together with failure to mention any preparation details is consistent with a teaching of a requirement for CD34+ stem cells. In total, the teaching of the specification does not give the skilled artisan clear instructions for what to do.

24. The population of bone marrow mononuclear cells used by Strauer (2002, of record) comprised only 2.1% CD34-positive cells (Strauer, p. 1914, paragraph bridging the columns). Similarly, as Applicant has pointed out (p.29, top) the Kornowski '832 patent teaches that "autologous bone marrow acts as a "natural source of mixed angiogenic cytokines" which "provide a mixture of potent interactive growth factors." Note, however, that Kornowski refers to "bone marrow" and to "the cells" in bone marrow, but not specifically to the *stem cell* population from bone marrow (column 4, lines 45-49). Kornowski discloses that cellular infiltrates in tissue after administration filtered bone marrow aspirates were 4-6% CD34+ (column 13, line 43-45). It is evident from Stauer and Kornowski that the critical cell in the preparations they administered may not be any previously characterized stem cell; it may not even be a *stem cell* at all but rather some other previously uncharacterized growth factor secreting cell.

25. The instant specification does not teach that there is anything critical about how to prepare bone marrow stem cells. The specification does not mention any requirement or criticality of using "unfractionated (global) bone marrow mononuclear cells". None of the terms "unfractionated", "global" or "mononuclear" are used, even once, in the specification. The specification does not even disclose the concept of using unfractionated or "the entire array of"

bone marrow mononuclear cells, let alone teach a method of using them. Therefore, there is no basis in fact for any arguments or assertions that the instant specification distinguishes over prior art, or that post-filing art confirms the instant teachings, on the basis of an alleged novel recognition that unfractionated bone marrow mononuclear cells can be used to grow an artery.

26. It has been established in the record and herein that Strauer considered the question of what cell population to administer to be of critical importance and that Strauer reviewed several papers published after the filing date of the parent '000 application in order form a procedural plan. It was in fact Isner '887 who made the discovery that the CD34+ mononuclear cell population, present in both bone marrow and peripheral blood, comprises progenitors for endothelial cells as well as the previously identified hematopoietic progenitors. Kornowski '832 and Isner '887 seem to be in general agreement as they each disclose cells derived from bone marrow as being able to stimulate neovascularization. The relationships among these cells remains uncertain, as is the precise population of cells that give rise to endothelial cells, as evidenced by Rabelink *et al.*, Arthrosclerosis and Vascular Biology, 24:834-838, (2004) at p. 835 (of record).

27. Further with regard to the choice of cell, Applicant argues that the Dohmann reference constitutes the best evidence because the process, materials, and results disclosed correspond to the claimed invention (Brief, p. 37). Dohmann provides autopsy proof that such heart repair involves artery growth, which is asserted to allay any challenge to the predictability of Applicant's "described heart repair by promoting artery growth through implanting BMC's" (Brief, p. 37). This is not persuasive, first, because Dohmann's process, materials, and results do not correspond to the claimed invention. Dohmann administered "autologous bone marrow mononuclear cells", which as detailed above, are not synonymous with "stem cells harvested

from bone marrow". "BMC" stands for "bone marrow cells" not "*stem cells* harvested from bone marrow". Dohmann acknowledged that it was not possible to identify the presence of stem cell descendents within the vessel wall or myocardium because the report was based on a single uncontrolled case involving late events after injection of unlabeled cells. Furthermore, given that the Dohmann paper was published in 2005, about seven years after the instant disclosure was first filed, any argument that it did not take extensive experimentation to achieve the reported results is untenable. As with the Strauer 2002 paper discussed above, Dohmann et al. relied upon basic preclinical research to design their study.

28. Applicant repeatedly asserts that the specification describes stem cells as being able to promote tissue growth or formation of an artery through "differentiation and morphogenesis" (Brief, p. 9, p.19, p. 25, p. 30, p. 35, p. 38, p. 39, p. 40). As noted above, Dohmann et al. acknowledged that their study was not designed to identify the presence of stem cell descendents within the vessel wall or myocardium. Ziegelhoeffer et al., (*Circulation Research*. 2004;94:230-238) studied the fate of GFP-labeled bone marrow cells transplanted into lethally irradiated recipients in a mouse model of hindlimb eschemia. The results showed that donor cells accumulate around growing collateral arteries and in ischemic tissues, but the donor cells do not become incorporated into endothelium or tunica media of the vessels. The authors concluded that bone marrow-derived cells do not incorporate into vessel walls, but may function as supporting cells (see Abstract). Therefore, even if Dohmann 2005, Strauer 2002, or other post-filing disclosures teach that administration of bone marrow cells causes the formation of an artery, the process is not through differentiation and morphogenesis as Applicant asserts. Thus, if Applicant's characterization of what the instant specification teaches is accepted, the post-filing

disclosures do not confirm these teachings, but instead the post filing evidence indicates that administered bone marrow cells, which would include some stem cells, do not differentiate into the cells of which arteries are made. In particular, the prediction that "if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (specification p.48, lines 13-15) has been shown not to be true when the source of stem cells is a mixed population of bone marrow cells and the organ under consideration is a new artery.

29. Applicant claims to be "the first to disclose and claim a method for human heart repair by implanting cells, such as stem cells, and growing a new artery" (Brief, p.36). To clarify the record, the following facts are noted. The instant disclosure was first filed as Application No. 09064000 on 4/21/1998. The first claim reciting administering cells in Application No. 09064000 was entered on 08/19/2004; the claims in that case do not recite repairing a heart. The earliest claim reciting administering cells to repair a heart in any continuing, divisional, or continuation-in-part of Application No. 09064000 was entered in the present application on 04/17/2001 (claims 36, 39, and 40). The first claims reciting "living stem cells harvested from bone marrow" were introduced in the present case on 11/21/2005. In contrast, WO/2000/057922, published October 5, 2000 included claim 1: "A method of enhancing collateral blood vessel formation which comprises the step of directly administering to a desired site an effective amount of autologous bone marrow." Dependent claims 3 and 4 recite injection of bone marrow intramyocardially, trans-epicardially or trans-endocardially. Note again that the agent recited for injection is accurately and precisely described as "bone marrow", which of course would include stem cells, but not "stem cells harvested from bone marrow". Thus, Applicant can assert the

earliest filing date, but Applicant is not the first to claim a method for human heart repair by implanting cells, such as stem cells, and growing a new artery. The U.S. national stage entry of WO/2000/057922 issued as U.S. Patent No. 7097832, Kornowski, of record.

30. The office action mailed 10/02/2008 cited two internet articles published in The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, entitled, "Tissue Engineering and Interventional Cardiology" and "Progenitor Cell Transplantation and Function following Myocardial Infarction." Applicant points out that the copies furnished by the Examiner contain less than the complete content of the published articles and argues that full consideration of omitted portions would not support the findings of the rejection of record. The Examiner acknowledges that the documents were incomplete due to a previously unrecognized error in converting the web pages to pdf format. The text of the rejection included a quote that was not reproduced on the copies provided (e.g. the final quote from participant O'Neill, "…bone marrow is unfiltered…Basically, the injection contains the "kitchen sink"…), which shows that the Examiner intended to provide the full documents. However, even when the complete documents supplied by Applicant are considered, it remains true that the concerns addressed by the participants in these discussions that took place about seven years after the instant specification was filed are the same as those raised herein and in the rejections of record with respect to the lack of guidance provided by the instant specification. It is clear that questions of choice of cell, dosing, timing, means of delivery, and cell survival, were still unanswered in these discussions that took place about seven years after the filing of parent application 09/064000. It remained uncertain what the critical cell in the preparations administered in the intervening art is; it may not be any previously characterized stem cell, it may not even be a *stem cell* at all but rather some other previously uncharacterized

growth factor secreting cell. The wisdom of transplanting an uncharacterized mixture of cells was in question (see comments by participants O'Neill, Dangas, and Holmes). The net effect of the multiple uncharacterized factors secreted by transplanted cells was still unknown and considered to be unpredictable (see comment by participant Dangas). Participant Witlow's comments are noteworthy if the selected site for growth of a desired artery is the heart and in view absence of any specific guidance as to how many cells to deliver in the instant specification; the non-toxicity of administered cells is apparently not predictable in the situation of attempting to repair a damaged heart, regardless of whether Dr. Witlow's concerns are ultimately substantiated or dismissed. These questions remained even though the participants were well aware of post-filing disclosures of record; Strauer was specifically cited. Clearly, considerable experimentation had taken place and several participants suggested that more experimentation was needed.

31. It was further noted that one of the participants in these discussions was Dr. Richard Heuser, a Declarant of record in the instant case. Applicant complains that the previous office action did not quote Dr. Heuser's comment "The first time I saw this technique presented by the group in Frankfort, I was astonished at how simple it actually was." It should be noted however, that Dr. Heuser went on to say, "Some of these therapies make good sense for the individual patient, but **more study data are needed**." Thus, Dr. Heuser apparently agreed with the preponderance of commentary, which indicates that the simplicity is more apparent than real. The rejection also posits that *if Applicant's arguments are to be accepted*, then Dr. Heuser, having "read and understood" the instant specification, was in possession of answers to the controversies under discussion. *If so*, Dr. Heuser could have clarified matters without divulging

any confidential information by directing his colleague's attention to Patent Application Publication 20040071637, which is identical to instant specification (as a continuation of 09/064000) and was published on April 15, 2004, or Patent Application Publication 20020192198, in which substantially similar disclosure was published on December 19, 2002, or Patent Application Publication 20030044396, in which substantially similar disclosure was published on March 6, 2003.

32. Applicant has asserted that "one skilled in the art would understand that except for injecting the stem cells into sites or adjacent to sites of ischemic injury, no further "manipulation" is required. Once the stem cells are implanted, they foci [*sic*] to the ischemic injury site via predetermined genetic pathways wherein differentiation and morphogenesis promotes the growth of new arteries" (Brief, p. 19). It is clear from the discussion published in The Journal of Invasive Cardiology, as well as from the other post-filing references of record, however, that many of the critical decisions, manipulations, and preparations take place before the injection is made. Clearly, simply knowing how to inject cells is not enough to perform a method of repairing a damaged heart or growing a new artery. Nevertheless, Applicant asserts that the claimed methods are enabled because "The specification discloses all the information that is needed for one skilled in the art to: 1) select bone marrow stem cells harvested from the patient; and 2) intramuscularly injecting said stem cells into sites of ischemic tissue for promoting differentiation and morphogenesis into new blood vessels, i.e., arteries (Brief, p. 35).

33. Therefore, this rejection finds that the post-filing references do not "confirm" the teachings of the instant specification, as asserted by Applicant. Instead, the post-filing references constitute evidence of the further act of invention that was required before achieving any growth

of an artery or repair of a heart. This rejection finds that the present application does not provide an enabling disclosure of or an accurate prediction of the methods and results that were later achieved by others. The following is focused on the specification as filed, and finds that it does not support the claimed methods with specific guidance. In fact the very concept of the claimed methods relies on selection of seemingly unrelated portions of the specification and putting them together, without specific prompting to do so.

34. Applicant asserts (Brief, p. 25): "The PTO posits, in the Office Action at pages 11-13, ¶16, that the specification does not provide "guidance for, or even suggest the use of bone marrow stem cells, any kind of stem cells, or cells of any kind, to grow an artery or repair a heart." Applicant responds by directing attention "to pages 47 and 48 of the specification wherein guidance is provided for forming soft tissue organs by direct differentiation and morphogenesis by reimplanting a patient's own cells, such as "growth of an artery" (page 48, line 3) which in "some cases [comprise] stem cells" (page 48, line 13)... Guidance for harvesting stem cells from the bone marrow of the patient for reimplantation to promote morphogenesis of soft tissue is provided on pages 40-42 of the specification." For convenience, the cited sections of the specification are reproduced here:

> Page 40, line 20 to Page 42, line 27
>
> > EXAMPLE 11
> >
> > MSX-1 and MSX-2 are the homeobox genes that control the generation and growth of a tooth. A sample of skin tissue is removed from the patient and the MSX-1 and MXS-2 homeobox gene(s) are removed from skin tissue cells. The genes are stored in an appropriate nutrient culture medium.
> >
> > BMP-2 and BMP-4 growth factors are obtained by recombinant or natural extraction from bone.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

MXS-1 and MXS-2 transcription factors are obtained which will initiate the expression of the MXS-1 and MXS-2 homeobox genes.

The MXS-1 and MXS-2 transcription factors, BMP-2 and BMP-4 bone morphogenic proteins, and MXS-1 and MXS-2 genes are added to the nutrient culture medium along with the living stem cells.

EXAMPLE 12

Example 11 is repeated except that the transcription factors bind to a receptor complex in the stem cell nucleus.

EXAMPLE 13

Example 11 is repeated except that the MXS-1 and MXS-2 transcription factors are not utilized. The transcription of the MXS-1 and MXS-2 homeobox genes is activated by applying an electric spark to the nutrient culture medium.

EXAMPLE 14

[0153] Example 13 is repeated except that the stem cells are starved and the transcription of the MXS-1 and MXS-2 homeobox genes is activated by applying an electric spark to the nutrient culture medium.

EXAMPLE 15

WT-1 and PAX genes are obtained from a sample of skin tissue is removed from the patient. The genes are stored in an appropriate nutrient culture medium. PAX genes produce PAX-2 and other transcription factors.

BMP-7 and other kidney related BMP growth factors are obtained by recombinant or natural extraction from bone.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

[The WT-1 and PAX genes, and BMP-7 and other kidney BMPS are added to the

nutrient culture medium along with the living stem cells.

A primitive kidney germ is produced. The kidney germ is transplanted in the patient's body near a large artery. As the kidney grows, its blood supply will be derived from the artery.

EXAMPLE 16

The Aniridia gene is obtained from a sample of skin tissue is removed from the patient. The gene(s) is stored in an appropriate nutrient culture medium.

Aniridia transcription factor (activates expression of the Aniridia gene) and growth factors (function to help stem cells differentiate during morphogenesis to form an eye) are obtained.

Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques. The stem cells are placed in a nutrient culture medium at 98.6 degrees. The temperature of the culture medium can be varied as desired but ordinarily is between 40 to 102 degrees F.

The Aniridia transcription factor and growth factors and the Aniridia gene are added to the nutrient culture medium along with the living stem cells.

A primitive eye germ is produced. The kidney germ is transplanted in the patient's body near the optic nerve. As the kidney grows, its blood supply will be derived from nearby arteries.

EXAMPLE 17

The Aniridia gene is obtained from a sample of skin tissue is removed from the patient. The gene(s) is stored in an appropriate nutrient culture medium.

Aniridia transcription factor (activates expression of the Aniridia gene) and growth factors (function to help stem cells differentiate during morphogenesis to form an eye) are obtained and added to the nutrient culture medium.

An eye germ develops. A branch of the nearby maxillary artery is translocated to a position adjacent the eye germ to promote the development of the eye germ. The eye germ matures into an eye which receives its blood supply from the maxillary artery.

Page 47, line 22 to Page 48, line 15:

> Organs and/or tissues can be formed utilizing the patient's own cells. For example, a skin cell(s) is removed from the intraoral lining of a cheek. The cell is genetically screened to identify DNA damage or other structural and/or functional problems. Any existing prior art genetic screening technique can be utilized. Such methods can utilize lasers, DNA probes, PCR, or any other suitable device. If the cell is damaged, a healthy undamaged cell is, if possible, identified and selected. If a healthy cell can not be obtained, the damaged cell can be repaired by excision, alkylation, transition or any other desired method. A growth factor(s) is added to the cell to facilitate dedifferentiation and then redifferentiation and morphogenesis into an organ or function specific tissue. Any machine known in the art can be used to check the genetic fitness of the organ and its stage of morphogenesis. A cell nutrient culture may or may not be utilized depending on the desired functional outcome (i.e., growth of an artery, of pancreatic Islet cells, of a heart, etc.) or other circumstances. Replantation can occur at any appropriate stage of morphogenesis. The foregoing can be repeated without the patient's own cells if universal donor cells such a germinal cells are utilized. Germinal cells do not require a dedifferentiation. They simply differentiate into desired tissues or organs when properly stimulated. Similarly, the DNA utilized in the foregoing procedure can come from the patient or from any desired source.
>
> During reimplantation one of the patient's own cells is returned to the patient. During implantation, a cell not originally obtained from the patient is inserted on or in the patient.
>
> In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.

35. These reproduced sections of the specification comprise the only references to bone marrow in the entire specification. The specification refers to bone marrow only in the sentence, “Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques", which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10; Examples 11, 15, and 17). These Examples assert that whole organs can be grown from bone marrow stem cells. Applicant apparently believes that the skilled artisan should take from these pages only the fact that they mention “cells” and “organs” but then ignore what they *actually say* about which cells to use, which organs to grow, or how to perform methods of using

the cells. In Examples 11-17 the artisan is instructed to remove genes from skin tissue of a patient and then the artisan is given the nonsensical instruction to store the genes in nutrient culture medium. (Actually, this instruction might make sense if one believes that nucleic acids and cells are not different from one another, as Applicant has repeatedly argued, e.g. Brief p. 26.) The genes are then to be added to culture medium along with stem cells; this apparently is meant to suggest a transfection procedure to genetically engineer the cells. This is taught to result in growth of a tooth, kidney, or eye, depending on the genes used. A cell that is capable of differentiation and morphogenesis to form an entire organ, such as an eye, would indeed be pluripotent, but bone marrow stem cells are not known to have this capability, even under the influence of an expressed Aniridia gene. These examples do not set forth credible procedures to produce the results asserted within the examples, and they do not even mention growth of an artery or repair of a heart as recited in the instant claims. Nevertheless, Applicant expects the skilled artisan to take the mention of bone marrow in the context of Examples 11-17 and combine it with the mention of "growth of an artery" (among other possible outcomes) on page 48 to arrive at enabling support for the instant claims.

36. Referring to Applicant's choice of pages 47-48, the section begins with a general statement that organs and/or tissues can be formed utilizing the patient's own cells. While one of skill in the art might expect that "patient's own cells" *could* refer to "stem cells harvested from bone marrow", among other possibilities, the next sentence steers the artisan away from that embodiment: "For example, a skin cell(s) is removed from the intraoral lining of a cheek." It is this skin cell that is the subject through all the description leading up to the mention of artery formation. The artisan is instructed to screen the skin cells for DNA damage, to check genetic

fitness, and repair damaged cells. No information is given as to what constitutes "genetic fitness", what genes are involved, or how cells are to be induced to affect the desired repair. The method then suggests the addition of some unknown and undefined growth factors after which the cells can undergo processes of dedifferentiation and redifferentiation followed by morphogenesis into any desired organ or tissue. No such growth factor regimen is known in the art, and the specification does not teach one. In view of the definition of "cell nutrient culture" (specification p.41), the instruction that, "A cell nutrient culture may or may not be utilized" refers to the potential use of novel combinations of growth factors, ECM, nutrients, and vitamins that are suggested to be able to cause cells to dedifferentiate, redifferentiate and form any organ or tissue. The specification, however, does not teach any specific factors or combination of factors that cause any cell to form an artery.

37. "Germinal cells" are suggested as an alternative to the dedifferentiated skin cells. The rejection of record has made the point that it is not clear what "germinal cells" are. In response, Applicant states (Brief, p.40) "While the Examiner may not understand what the term "germinal cell" includes, those skilled in the art are aware that a germinal cell is a cell which divides into other cells. In plain terms, a germinal cell is a cell that is capable of differentiating. Thus, the language "germinal cells (and in some cases, stem cells)" clearly defines cells that are capable of direct differentiation and morphogenesis into an organ, e.g., pluripotent cells capable of inducing growth of multiple tissues." This misses the point. The term "germinal cell" is generally understood to refer to a cell from which other cells proliferate, but this functional definition does not guide the artisan as to where or how to obtain the cells that can be used to grow an artery or

any other organ. Consider the effect of substituting Applicant's definitions into the specification in place of "germinal cells":

> The foregoing can be repeated without the patient's own cells if universal donor cells such as *cells which divide into other cells* are utilized. *Cells that are capable of differentiating* do not require a dedifferentiation. They simply differentiate into desired tissues or organs when properly stimulated…. In the example above, if *cells that are capable of differentiating* (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.

38. This certainly does not provide the skilled artisan with any clear instruction of what to do. The specification essentially instructs the skilled artisan to grow an organ by using a cell capable of growing an organ. Clearly, "germinal cells" does not refer to a specific kind of cell. The context indicates that "germinal cell" is meant to connote something distinct from a stem cell—"germinal cells" and "stem cells" are presented as alternatives connected by "or", not as synonyms or related as genus and species. "Germinal cells" are suggested to differentiate into desired tissues if properly stimulated. How to properly stimulate them to form an artery or any other organ is not disclosed.

39. In summary, pages 47-48 of the specification suggest the examination of fitness of unknown genes by unidentified criteria, the use of unidentified machines, unknown methods of effecting DNA repair, the addition of unknown and undefined growth factors, ECM components, nutrients, and/or vitamins to cause cells to undergo dedifferentiation, redifferentiation, and morphogenesis into *any desired organ or tissue*, and unidentified "germinal cells". These teachings are found to be inadequate for teaching the skilled artisan to *how to* grow an artery. Furthermore, the skilled artisan is required, according to Applicant's argument, to ignore all of this description of what to do with a skin cell and infer that the "patient's own cells" in the first sentence refers to stem cells harvested from bone marrow.

40. While pages 47-48 suggest that stem cells can be used "in some cases", the specification does not specifically teach that stem cells should be used to grow an artery. While the hypothetical dedifferentiated skin cell and/or "germinal cells" might be pluripotent, they are not species of stem cells harvested from bone marrow, they are not species of any known stem cell, there is no evidence that they even exist, and the "guidance" does not teach one of skill in the art as to how to use them in the instantly claimed methods. In order to arrive at the claimed methods, one first has to select "growth of an artery" from among the several possible outcomes suggested, select "new portion of a pre-existing heart", and then guess that the "some cases" where stem cells are utilized (p.48, line 13) refers to instances where one wishes to grow an artery in a dead or damaged heart. Even if that guess is made, no particular reason is given why the stem cell should be harvested from bone marrow—bone marrow is not mentioned in the context of artery formation or heart repair. Since the artisan is required to look elsewhere in the specification for guidance as to which cell to use, there is no particular reason to not choose "the blood of the patient, or from cell culture techniques" (see pp. 40-42). The artisan could look to p.37, lines, 19-23, which teaches:

> "Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated. Likewise, any host cell, cloned cell, cultured cell, or cell would work."

41. Far from guiding the skilled artisan on how to perform a specific method, the most straightforward meaning of this teaching is that the skilled artisan should believe that any cell can do anything. Applicant asserts that this was not intended meaning (Brief, p. 39). It is indeed not clear what "work" means. The immediate context is eye formation (p. 37, lines 17-18), but

the general context seems to be about formation of any desired tissue. The nearest mention of "artery" occurred two paragraphs preceding, on page 37, lines 8-16 (emphasis added):

> "Sticky cells can be used to attach genetic implants to selected sites. This is, for example, important when placing a soft tissue implant in or on a site of an *artery* wall. In this manner, an additional heart could be grown from a genetic implant. Once matured to a reasonable state, this new heart can be the body's primary heart and the old heart can be evacuated surgically. Any venous or *arterial* connections, reconfigurations, or ligations can be surgically attended to. Any other organ can be similarly produced at any desired site in soft or hard tissue."

42. Therefore, page 37, lines, 19-23 can be understood (if the malapropism of "cascade of genetic material" is ignored and the expression is taken to be equivalent to "genetic cascade") to suggest that the combined action of a hypothetical master control gene together with stem cells or "germinal cells" can result in the formation of any desired tissue. This is clearly not a specific teaching about artery formation. Therefore in this context, the sentence "Likewise, any host cell, cloned cell, cultured cell, or cell would work" would have the skilled artisan believe that any cell can be made to form any tissue, which teaches away from any suggestion to specifically use stem cells to form an artery.

43. Finally, even if Applicant's desired choices were made, so that use of stem cells to grow an artery is contemplated, the specification does not teach one of skill in the art *how to* use stem cells to grow an artery—as noted above, this section does not even teach how to use the explicitly exemplified skin or germinal cells to form an artery. The specification tosses out the idea that something can be done and then invites the skilled artisan to figure out how to do it. It should be emphasized again that the prediction that "if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (p.48, lines 13-15) has been shown not to be true when the source of stem cells

is a mixed population of bone marrow cells and the organ under consideration is a new artery (see Ziegelhoeffer et al., (*Circulation Research* 2004;94:230-238).

44. The rejection of record finds that Examples 18, 19, and 36, which are directed to administration of VEGF165 cDNA, do not even suggest the use of bone marrow stem cells, any kind of stem cell, or cells of any kind, to grow and artery or repair a heart, much less provide guidance for the use of bone marrow stem cells for these purposes. Applicant has generally argued that one of skill in the art would view "stem cells" and "VEGF cDNA" as species within a larger genus of "growth factors" as defined in the specification, an thereby be prompted to substitute stem cells for the VEGF cDNA in Examples 18, 19, and 36. Applicant cites an excerpt from the February 22, 2006 Office Action for co- pending application Serial No. 09/794,456: "The claims are being examined to the extent that they read on the elected invention, administration of cells, and thus the generic concept of growth factor is not relevant" as evidence to argue that the PTO has failed to review the application disclosure in its entirety (Brief, p.11).

45. Applicant's use of the term "growth factor" has been addressed in the office action mailed 10/02/2008. The instant specification puts forth a genus of "growth factors" that includes, apparently, all of the molecules that are generally recognized as growth factors, plus all of the genes encoding such molecules (although genes are not mentioned in the definition on pages 20-21 of the specification), plus all living organisms, and unspecified organic and inorganic matter. Applicant asserts that "living organisms" implicitly includes all kinds of cells, but "cells" or "stem cells" are never explicitly set forth as species of growth factor anywhere in the instant specification. The expression "growth factors, such as stem cells" does not appear anywhere in the specification, it is never found in peer-reviewed non-patent literature, or in any patent

literature; it only appears in arguments of counsel in this case and others with the same applicant. The office action mailed 10/02/2008 included extensive evidence from medical dictionaries, textbooks, and literature searches, to show that use of the term "growth factor" to mean "cell" (or "cell" to mean "growth factor") is outside of the normal meanings of these terms (¶¶20-23). Therefore, this rejection maintains that the specification as filed does not provide specific prompting for one of skill in the art to read "VEGF cDNA" (as in Examples 18, 19, and 36) and think "stem cell".

46. In view of the presented evidence, Applicant now argues:

> "The PTO's arguments raised at pages 16-19, ¶¶20-23 of the Office Action are moot in regard to Appellant's elected invention cells and more specifically stem cells presently on appeal" (Brief, p. 27).

47. The designation "moot" is allegedly supported by prior restriction requirements in the present case, by "numerous restriction requirements between "gene" and "cell" growth factors have been consistently made by the PTO", and by one such restriction requirement in continuation application Serial No. 11/605,153 filed November 28, 2006. Applicant further argues:

> "the term "growth factor" as used by Appellant in the context of the described and claimed invention is defined on page 20 of the instant specification as comprising a composition which promotes the growth of soft tissue, and specifically, as an angiogenesis promoter for artery growth… Moreover, Dr. Isner, as well as Declarants Drs. Richard Heuser and Andrew E. Lorincz, recognized that both cells and genes promote soft tissue growth. Both DNA encoding VEGF and EC progenitor cells are described by Isner '887 as promoting the growth of soft tissue, capillary blood vessels. Clearly, one skilled in the art apprised of the teachings of Isner '887 relating to the properties of both genes and cells when reading the instant specification would find ample guidance for injecting either DNA encoding VEGF or cells, such as stem cells, for promoting the growth of arteries to treat ischemic tissues in humans." (Brief, p. 28-29)

48. This is not persuasive for several reasons. First, if one is prompted by claims reciting cells to be a species of growth factor, it is easy to perceive that Applicant intends that cells should be considered as a species of growth factor. Such claims are present in continuation application Serial No. 11/605,153. Such claims were given to the Declarants of record in the present case. Such claims were not present in the instant application as filed. It is a separate question whether the specification as filed supports the claimed concept and it is yet another whether question as to what extent the said concept, if present in the specification, enables one of skill in the art to make and use the claimed invention. The latter question is the issue at hand. The rejection of record explicitly stated that the point is not that it is abhorrent or technically incorrect for the Applicant to attempt to define a class of growth factors that includes genes, cells, or specifically bone marrow stem cells. To elaborate on the quotation from the February 22, 2006 Office Action, Applicant's definition of "growth factor" is "not relevant" because it is not effective to guide the skilled artisan in performing the claimed methods involving administration of the elected species of cells.

49. This finding does not violate or contradict any past or present restriction requirement in this application or any related application. The restriction requirement indicates that that cell therapy and gene therapy are not obvious variants of one another, as indicated, for example, by their separate classifications. It follows that an example directed to gene therapy would not make obvious, or implicitly suggest a method of cell therapy. Any such suggestion would need to be explicitly made. Even if it can be deduced that both "VEGF cDNA" and "stem cells" can promote the growth of hard tissue, such as bone, or soft tissue, in the body of a patient, thereby placing them both within the definition of "growth factor" given in the specification, the

specification as filed does not provide specific prompting for one of skill in the art to read "VEGF cDNA" (as in Examples 18, 19, and 36) and think "stem cell". The circuitous line of reasoning leading from "VEGF cDNA" to "growth factor" to "stem cell" requires the skilled artisan to perceive that the specification intends the broadest definition "growth factor", which includes "living organism", and then select the subgenus "cells" from the genus of "living organisms", and then to further select subgenus "stem cells". The requirement for this indirect line of reasoning does not provide a justification for asserting that any time any growth factor is mentioned, the skilled artisan is prompted to apply the teaching to cells in general, or specifically to stem cells.

50. Applicant cites Isner '887 as evidence that those skilled in the art prior to the 1998 filing date were aware that EC progenitor cells (a type of stem cells) and DNA encoding VEGF are alternative angiogenesis promoters for treating blood vessel injuries, i.e., ischemic tissue. This logic is tenuous because Applicant has repeatedly claimed to have used different cells and achieved a different result than Isner '887. Although Examples 18, 19, and 36 teach administration of a VEGF cDNA expression plasmid, apparently modeled (without attribution) after that in Isner et al., (*Circulation.* 1995; of record), the Examples also prophetically describe artery growth, which was not observed in Isner et al., (1995), Isner '887. Furthermore, the process of arteriogenesis described in Examples 18, 19, and 36 is mechanistically at odds with the prevailing understanding in the art, as discussed herein. Thus, Applicant is arguing that prophetic examples that predict unprecedented outcomes for a single species, VEGF cDNA, should be extrapolated across the entirely of a huge genus, at least including a particular additional species (bone marrow stem cells) which Applicant wishes to claim. Since the plasmid

in Examples 18, 19, and 36 is achieving unprecedented results, it does not necessarily follow that one of skill in the art would expect to find a cell with equivalent capability, even with Isner '887 and Asahara (of record) as guidance. It does not follow that because endothelial progenitor cells (Isner '887 and Asahara) are capable of promoting capillary growth, it is predictable that "a growth factor", "a cell", "a stem cell", or "a living stem cell harvested from bone marrow" will form a new artery thereby causing a heart to be repaired.

51. The Isner and Asahara disclosures merely make it plausible to propose that cell populations with broader and more robust capabilities to form blood vessels, or specifically arteries, might exist. As stated in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

52. If the skilled artisan guessed that there might be a cell analogous to the EC progenitor of Isner '887, but with arteriogenic capability like the plasmid in Examples 18, 19, and 36, the artisan would need to turn elsewhere in the specification to find the cell. The artisan would find the following: (1) Pages 47-48 teach that "a patient's own cells", for example a skin cell that has undergone a mysterious process of dedifferentiation and redifferentiation, or "germinal cell or in some cases stem cells" may be used to grow organs such as an artery, (2) Page 37, lines, 20-23, which teaches that, "any host cell, cloned cell, cultured cell, or cell would work" like

"Multifactorial and nonspecific cells (such as stem cells and germinal cells)", and (3) Pages 40-42, which mention "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques" in the context of incredible methods for growth of a tooth, kidney, or eye, depending on the genes used to transform the stem cells. If the right choices are made, the artisan arrives at the concept of the instant claims.

53. Therefore, the most Applicant can say about the instant disclosure is that, by circuitous logic not explicitly presented in the disclosure, one of skill in the art might surmise that a method to use autologous stem cells to grow an artery was suggested. For example, the Declarants of record have been willing to say: "The disclosures referenced in above Paragraph ... of the specification *relate to* using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery" (emphasis added)." According to the Declarations, this general conclusion was based upon reading juxtaposed excerpts of the specification (not the complete specification) together with claims reciting administration of stem cells, which were not original to the application as filed. With regard to the enablement requirement, the appropriate factual determination is whether the instant specification reasonably directs one skilled in the art how to *make and use* the claimed subject matter. A disclosure that makes it possible to piece the claimed generic concept together is not the same as an enabling disclosure. As was found in *Ex parte Hitzeman*, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); *Amgen Inc.*

v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present specification does not disclose even a single enabled embodiment of the claimed method. The instant specification does not show a single organ, part of an organ, tissue, artery, or even a bud, formed by placing cells in a body.

54. Further regarding the value of Examples 18, 19, and 36 in guiding the use of stem cells in the claimed methods, Applicant (Brief, pp. 30-34) addresses the question of calculating a dose of cells to use. Appellant submits it is clear from MPEP Section 2164.01 (c) that it is not necessary to specify the dosage if one skilled in the art could determine such information without undue experimentation. The Examiner agrees that, by itself, the presence or absence of guidance as to how many stem cells should be used to grow an artery would not answer the question of whether the instant disclosure satisfies the requirements of 35 U.S.C. 112, first paragraph. However, if present, a recommended dosage would be understood as guidance to be considered along with the other factors in the enablement analysis.

55. Applicant argues that Examples 18, 19, and 36 not only suggest the use of stem cells to grow an artery, they provide guidance in the number of cells to use, Applicant has refrained from repeating the assertion that the specification describes new artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25×10^6 (Example 18 & 36) to approximately 12.5×10^6 (Example 19), but instead posits that these values are readily obtained because one of skill would extrapolate an appropriate cell number from the quantities of plasmid DNA taught in the Examples (Brief, p.31). Thereafter, Applicant's arguments are duplicative of arguments that have been addressed thoroughly in the record, particularly in the office action mailed 10/02/2008 at paragraphs 24-33.

56. Examples 18, 19, and 36 do not mention cells of any kind. A method for deriving these cell numbers is not in the specification as filed. A specific method for making this extrapolation was first entered the record in this case only in arguments of counsel. Thus, to arrive at the 6.25 x 10^6 and 12.5 x 10^6 cell numbers, one of skill in the art would first need to read Example 18 and perceive a suggestion to use stem cells, even though Examples 18, 19, and 36 do not even mention cells of any kind, and then derive the method of converting the amount of plasmid DNA to a number of cells to use presented in the Brief, p. 32-33 footnote. The footnote, and the text on page 32, states, "using 2,000 micrograms as a preferred dosage of nucleic acid described by Isner '887 one skilled in the art applying Appellant's calculus could extrapolate to a cell dosage of about $50x10^6$, which falls within the range specified for cells by Isner '887". This ignores the fact that .Isner teaches: "Effective amounts of DNA are between about 1 and 4000 μg, more preferably about 1000 and 2000, most preferably between about 2000 and 4000", and "Generally, from about 10^6 to about 10^{18} progenitor cells are administered to the patient for transplantation" (column 11, lines 4-9 and column 7, lines 17-23, respectively). Note that Isner teaches a 4000-fold range of μg DNA and a *trillion-fold range* (10^6 to about 10^{18}) of cells. This shows that even if using the amount of plasmid DNA to calculate a number of eukaryotic cells were a legitimate procedure, the formula for doing so could not be the simple ratio Applicant has presented if the formula is based on Isner's numbers. This supports the rejection of record which finds that any relationship between the results of Applicants formula and any cell number taught in Isner '887 or in any post-filing art is coincidental. It is neither surprising nor convincing that a formula could derive a value with this trillion-fold range. Furthermore, there is no evidence that

Isner saw any significant relationship between the disclosed amounts of plasmid DNA and numbers of cells.

57. Applicant (Brief, pp. 32-33) asserts that "The Third Supplemental Declaration of Dr. Richard Heuser (of record and originally filed in co-pending application Serial No. 10/179,589) and the Second Supplemental Declaration of Dr. Andrew E. Lorincz (of record and originally filed in co-pending application Serial No. 10/179,589) confirm and establish as a fact that the extrapolation was long known in the art and Appellant's reliance thereon is reasonable." Applicant refers to said Declarations, "Appellant's evidence establishes as a material fact that physicians have long used conversion charts/formulas for estimating dosages of cells from nucleic acids and vice versa." These Declarations have been addressed in the record. The conversion charts and methods referred to by Drs. Heuser and Lorincz, and which Applicant cites as having been employed in the medical art for decades, are methods wherein *an amount of cellular DNA is used to calculate a number of cells of the same species as the source of DNA*. In contrast, the extrapolation under discussion attempts to convert *an amount of a plasmid DNA construct to a number of stem cells*. Plasmids are found natively in bacteria, not human stem cells. Therefore, the conversion under discussion is fundamentally different from the extrapolations discussed by the Declarants, because it crosses species lines. Furthermore, a *plasmid DNA construct* is designed to express a single desired gene, which is quantitatively and qualitatively different from genomic DNA as it is found in cells. Every molecule of the postulated plasmid DNA comprises a copy of the VEGF cDNA. In contrast, VEGF coding sequences would comprise but one of 30-40 thousand genes in genomic DNA (at the time of filing, it was widely believed that the human genome comprised 100,000 genes). According to

the data from tables supplied by Drs. Lorincz and Heuser, it has been shown in the record that the amount of VEGF coding sequence in an equal mass of human genomic DNA and VEGF plasmid DNA differs by a factor of 5.26×10^5. Therefore, it is fundamentally illogical to equate recombinant plasmid DNA to cellular DNA on the basis of mass. It has also been established in the record that scientists 50 years prior to the filing date of the instant application (the time period cited in the Declarations at paragraph 6) would not recognize the terminology or even imagine the concept of the plasmid-to-cell conversion under discussion because plasmids had not been discovered, the term 'plasmid' had not been coined, and the methods for making and using constructs comprising plasmids and cDNA had not been developed. It is, therefore, impossible any argument that such extrapolations have been used for decades in the medical arts in regard to cell therapy to be true. All of this has been presented to Applicant in previous office actions. The Declarants did not address these issues. Applicant has declined to present an argument to refute this.

58. It has been pointed out in the record, that this aspect of the rejection could be refuted if an example of an extrapolation like the one in question were found in the peer-reviewed scientific literature or the patent literature. No such example has been found.

59. Applicant has pointed out that MPEP Section 2164.01 (c) states that it is not necessary to specify the dosage if one skilled in the art could determine such information without undue experimentation. Although the cell dosage was mentioned in an early formulation of this rejection (office action mailed 12/09/2004), cell dose has never been cited as single, critical factor for determining enablement. Applicant has argued the bone marrow cells are generally considered to be non-toxic and it is difficult to overdose while using them (Brief, p. 29, p. 32,

p.34). In the face of this, one might ask why Applicant has chosen to bring the calculation presented in the footnote on pages 32-33 of the Brief into the discussion. The answer appears to be that Applicant seeks to persuade the Examiner, or the Board, that the specification is far more definitive in its teaching than it actually is. It is clear from the facts presented herein and in the rejections of record, that the method under discussion, which purports to extrapolate an appropriate cell number for administration from the quantities of plasmid DNA, is Applicant's *post hoc* derivation. It is not present in the application as filed. It is not implicit in the teachings of the specification. It is not substantially analogous to well known methods of converting DNA amounts to cell numbers within a species cited by the Declarants. It is not information that is already known by those skilled in the medical arts. There is no example of it in the prior art or post-filing art. There is no rational basis for proposing that a person of skill in the art at the time the instant application was filed would even think of doing it without being specifically prompted to do so. The instant specification does not provide that prompting.

60. Regarding the presence or absence of working examples in the specification, it has been noted in the record that the present specification does not disclose even a single enabled embodiment of the claimed method. The instant specification does not show a single organ, part of an organ, tissue, artery, or even a bud, formed by placing cells in a body. Applicant's Brief addresses the issue of examples on pages 35, 40, and 41. Applicant generally argues that working examples are not required. Applicant asserts (Brief, p. 35):

> "At page 27, ¶37 of the Office Action, the PTO puts forth the proposition that there is a higher "enablement" standard required by the statute for "cases that involve unpredictable factors such as most chemical reactions and physiological activity" while citing case law presumably "codifying" such a higher standard. In other words, the PTO is placing a

> higher burden on Appellant to support enablement because of the nature of the claimed invention. The PTO is relying on case law because the first paragraph of §112 does not embody such a separate requirement for chemical and physiological related inventions vis-a-vis other classes of inventions. What is certain is that the question of enablement must be determined on a case-by-case basis taking into consideration the facts presented."

61. This is not persuasive because, first, as a practical matter the Examiner cannot simply ignore the relevant case law. The cited case law was established precisely by determining enablement on a case-by-case basis taking into consideration the facts presented. Likewise, the instant application is being considered by taking into consideration the facts presented herein. In this regard, it is noted that Applicant has repeated the assertion that U.S. Patent No. 7097832, Kornowski, contains claims drawn to a cell therapy treatment of humans requiring the implantation of bone marrow stem cells in the heart to grow collateral blood vessels based on a prophetic disclosure (Brief, p. 35 and p. 41). Applicant had previously cited the Kornowski '832 patent to allege that the instant rejection is not consistent with PTO practice wherein prophetic examples were deemed to be sufficient to support the allowed claims. Applicant now emphasizes that the Applicant referred to the claims in Kornowski '832 as being drawn to treating humans as prophetic, not to challenge the enablement of such patent (Brief, p. 35). This is understood. Applicant's argument has been addressed in the record and has been found to be not persuasive. The examples that support the allowed claims in the '832 patent are not prophetic because they are based on work actually performed and results actually achieved. See MPEP 2164.02. The examples in the '832 patent are "prophetic" only in that the methods were not demonstrated in humans. It has been stated explicitly in the record that the USPTO cannot, and does not, demand human clinical trials to demonstrate enablement for claims to methods of treating humans. Nothing in the rejections of record can logically be taken to imply such a demand. Patents in

which biotechnological inventions are directed to the treatment of humans may rely on animal, or even in vitro, evidence that the claimed methods are supported by a sound scientific basis, that the methods can work, and to provide enough guidance so that application to humans can proceed with a reasonable expectation of success. The sufficiency of the evidence is determined on a case-by-case basis. The instant specification provides no evidence comparable to that in the Kornowski '832 patent upon which to base a judgment.

62. With respect to compliance with 35 USC 112, first paragraph, the entire claim has weight, including statements of purpose and intended outcome recited in the preamble or in 'wherein' clauses. Therefore, in the instant case, the claims must be enabled for forming and artery, growing new cardiac muscle, and repairing a dead or damaged portion of a heart. Questions of which cells to use, how many to use, when to administer the cells, and whether the disclosed results are confirmed by post-filing disclosures might have been clarified by working examples in the specification. Even the prophetic examples are not specifically directed to the claimed subject matter. The absence of specific examples is a contributing factor because a prophetic example based on predicted results rather than work actually conducted can support enablement only if the claimed results are actually predictable. Case law cited in the record confirms that chemistry, biology, medicine, and physiology have been consistently recognized as unpredictable arts. It has been established herein and in the record that Examples 11-18, 19, and 36, cited by Applicant as supporting the enablement of the instant claims, not only lack support by experimental evidence, they prophetically teach unpredicted, even incredible, results. It has been established herein and in the record that post-filing disclosures show that extensive experimentation has been required to achieve results that fall within the scope of the asserted

claims. Regardless of how straightforward the practice of the claimed invent may be, the instant specification does not establish with any reasonable certainty how to select the cells that will form an artery and repair a heart, or whether administration of any of the cells mentioned in the specification will form an artery or repair a heart. The instant specification asserts many remarkable results but does not show a single organ, part of an organ, tissue, artery, or even a bud that has been formed by merely placing cells in a body. The present specification does not disclose even a single enabled embodiment of the claimed method. Thus, Applicant's assertion (Brief, p.14) that "the materials and administration techniques, but not the inventive results, were well known when the instant application was filed" is not persuasive: There are no inventive results.

63. On pages 46-50 of the Brief, Applicant again alleges that the Declarations of Dr. Meger, Dr. Heuser and Dr. Lorincz had not been given due consideration. The experts have given *an opinion as to the ultimate legal conclusion of enablement*, to which no weight is given. Case law has established that anticipation and operativeness are questions of fact; however, obviousness and enablement are questions of law. See In re Lindell, 155 USPQ 521; In re Chilowsky, 134 USPQ 515. The underlying basis for the legal conclusion has been considered herein and in the record. For example, Applicant asserts that "Declarants identify and rely upon specific disclosure in the instant specification which supports their conclusions that one skilled in the art would be able to carry out the claimed invention." As stated herein, the Declarants of record have been willing to say: "The disclosures referenced in above Paragraph ... of the specification *relate to* using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery" (emphasis added)."

That is, the Declarants managed to piece the general idea of the instant claims together. According to the Declarations, this general conclusion was based upon reading juxtaposed excerpts of the specification (not the complete specification) together with claims reciting administration of stem cells to grow an artery, which were not original to the application as filed. A disclosure that makes it possible to piece the claimed generic concept together is not the same as an enabling disclosure. It is easy to predict that if one injects cells into a body, *something* will grow therefrom; it might even be an artery—even tumors have arteries. Such a prediction however, does not meet the legal standard for enablement. As stated in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

64. The sections of the specification cited in the declarations have been thoroughly considered, along with the entire disclosure, herein and in the record. The thread that connects the pieces of the generic concept also runs through hints of non-existent methods, unidentifiable cells, nonsensical method steps, and most importantly, predictions of results that are either incredible or directly contradicted by subsequent disclosures. Besides not having legal weight, Declarants' conclusory statements regarding predictability and the amount of experimentation required are thoroughly refuted by the references cited herein and in the record. Even though

administration of cells, and apparatus therefor, were known in the medical art at the time of the present invention, the evidence presented herein and in the record shows that simply knowing how to inject cells is not enough to perform a method of growing a new artery or new heart tissue. The choice of cell to be administered to achieve the recited outcome was not known in the prior art, it is not clearly described in the specification, and it remains a subject of controversy long after the instant disclosure was filed. Therefore, the Declarations of record are not sufficient or convincing to overcome the instant rejection.

65. Applicant (Brief, p. 50) compares the instant case to *in re Wands*, generally arguing that the "instant fact situation is similar to that of *In re Wands* because the skill level is also high and known administration techniques and known materials are also utilized in the practice of the invention." Applicant again refers to the expert opinion declarations of Drs. Heuser and Lorincz. Applicant urges that proper consideration of all of these factors compels a conclusion that undue experimentation would not be required. This has been fully considered but is not found to be persuasive. In *Wands*, the sole issue was whether, in that particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies against HBsAg (*In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1404). The facts showed that **inventor Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations** (*In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1407). The court ruled that that it would not require undue experimentation to make and use the claimed immunoassay method. The court in *Wands* stated that enablement is not precluded by the necessity for some experimentation such as routine screening. (*In re Wands*, 8 USPQ2d 1400 at p. 1404). The facts in the present case are substantially different from those of

Wands. In the instant case, what is missing is well beyond routine screening. Unlike the monoclonal antibody art, the art of stem cell therapy is not as highly developed and success is not predictable. The specific outcomes recited in the instant claims are unprecedented and the record shows that extensive experimentation has been performed by others in order to achieve methods that fall within the scope of the instant claims. The working examples in *Wands* were deemed sufficient to provide adequate guidance in view of the skill in the art and the already advanced development of the technology (*In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1406). In contrast, the instant specification presents no working examples directed to the claimed methods, as noted herein and in previous office actions. The prophetic examples not only lack support by experimental evidence, they predict results that are either incredible or directly contradicted by subsequent disclosures. Therefore, the only *Wands* factor weighing in favor of enablement is the level of skill in the art, which is relatively high. It follows that, unlike *Wands*, the instant disclosure does not enable the skilled artisan to make and/or use the claimed invention without undue experimentation.

66. The rejection of record had cited See *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997) in which the Court stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." The rejection finds that the notion that the claimed new results, artery growth and repair of a damaged heart, can be achieved using old materials (bone marrow stem cells) and old

methods (injection), was *at best* "a germ of an idea" at the time the instant application was filed. In response Applicant offers the following definition of "a germ of an idea:

> If the specification had done no more than to generally suggest that the use of some unidentified composition could grow soft tissue, such cardiac muscle and an artery in a human patient, such general suggestion would constitute tossing out a germ of an idea (Brief p.46).

67. It is first noted that in view of Applicants broad definition of "growth factor", claim 236, effectively recites the use of "some unidentified composition" to grow soft tissue, such as cardiac muscle and an artery in a human patient. Thus, claim 236 fits Applicant's own definition of "a germ of an idea" very closely. Furthermore, The Declarants Dr. Lorincz and Dr. Heuser of record have concluded the following:

> I note that the disclosures referenced in above Paragraph 4 relate to using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery. [emphasis added]

68. Thus, the Declarants' assessment is very similar Applicant's "germ of an idea". The germ has sprouted in that the "unidentified composition" of has become "a cell, such as a stem cell". The instant specification does no more than generally suggest the use of a cell to grow cardiac muscle and a new artery (if that). Therefore, although "a cell, such as a stem cell" is more precise than "unidentified composition", the concept remains a germ of an idea. The instant specification does not even clearly enunciate this germ of an idea, let alone provide an enabling disclosure of how to make and use the claimed invention. The instant specification provides no basis for distinguishing artery growth and repair of a damaged heart from any of the incredible outcomes that are also asserted in the specification, such as growth of an entirely new eye, kidney, or heart. Even if artery growth is perceived as more plausible because of the relative simplicity of arteries

as compared to the other organs, "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis." Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005). *At best*, the claims under consideration represent guesses. The post-filing references of record are not confirmation of the claimed results, but rather they are evidence of further experimentation involved in the act of invention.

69. The rejection of record has given careful consideration to the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the level of skill in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. It has been acknowledged that the level of skill in the art is high. However, the remaining factors indicate that the each of the claims under consideration must be rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Conclusion

70. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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